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Title:	w18_empower-aids - HIV Envelope at Multiple Scales
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Intended for:	IC report
Issued:	2019-03-04

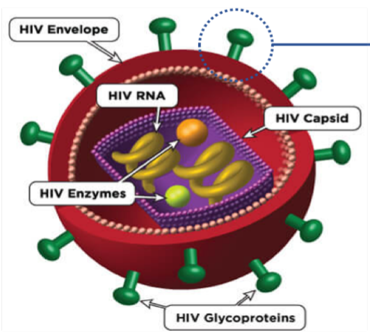
IC report viewgraphs for:
w18_empower-aids - HIV Envelope at Multiple Scales

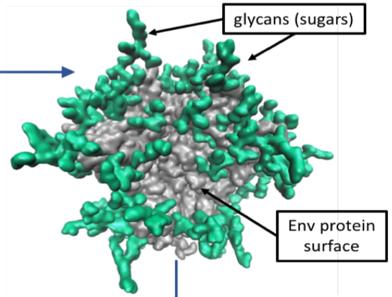
Abstract:

Being the sole viral protein entity expressed on the surface of the Human Immunodeficiency Virus (HIV) envelope, the Envelope Glycoprotein (Env) remains the only plausible immunological target. Nevertheless, extreme dynamic heterogeneity, structural complexity, and system size make the study of these glycoproteins immensely challenging. We have utilized the Institutional Computing (IC) resources to overcome some of these challenges in computational modeling of the Env glycoproteins. This integrated technique can sufficiently sample a physiologically relevant conformational space accessible to carbohydrates, in a very short time. This method has been validated by quantitatively comparing to experimental cryoEM maps of the HIV Env protein. We have employed graph theory to capture the glycan shield topological network, pinpoint potential interaction pathways, and identify concerted behavior of the glycans. Analyses of various network attributes, such as relative centrality of different glycan positions, identification of communities, and critical subnetwork features, have aided in detailed examination of the glycan shield. Starting from select structures modeled by the pipeline, we are performing large-scale atomistic MD simulations to study the temporal behavior of this system, which will help elucidate biologically relevant antibody behavior. This method can be seamlessly extended to benefit research in Zika, Ebola and other high-density glycosylated systems.

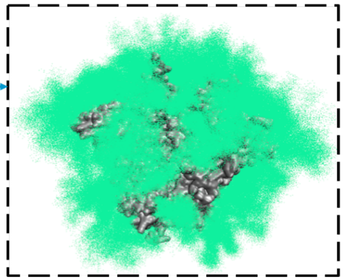
w18_empower-aids: HIV Envelope at Multiple Scales

The HIV virus and envelope protein (Env)



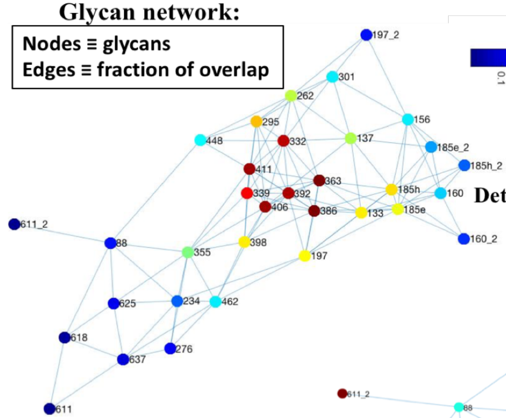


Cumulative shielding effect over time due to dynamic nature of glycans

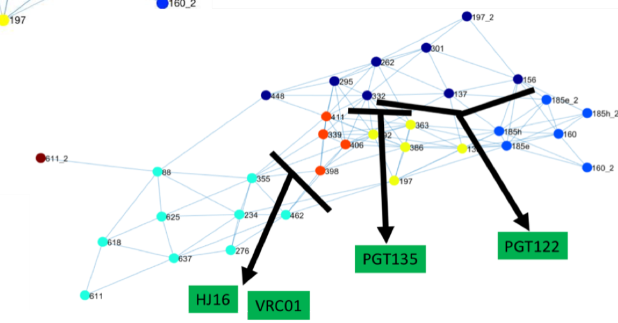


Env: only viral protein on the surface; therefore, major target for current HIV vaccine efforts

Immunologically relevant local and global properties of glycan shield



Detecting communities of glycan subdomains by modularity maximization



Community boundaries are more susceptible to antibody binding

High-throughput pipeline to generate glycan ensemble at atomistic level

All-atom structural model of protein generated using homology modeling

↓

Assess the quality of the models

↓

Ab-initio modeling of glycan chains at each known site with ideal geometries from CHARMM forcefield with random orientation

↓

1 Å randomization of glycan atomic coordinates

↓

Structures relaxed with conjugate gradient steps and simulated annealing

↓

Ensemble of 1000 different conformations built for each model

Optimizing the objective function:

$$V = \sum_{bonds} k_b(b-b_0)^2 + \sum_{angles} k_\theta(\theta-\theta_0)^2 + \sum_{dihedrals} k_\varphi[1+\cos(n\varphi-\delta)] + \sum_{impropers} k_\omega(\omega-\omega_0)^2$$

$$+ \sum_{Urey-Bradley} k_u(u-u_0)^2 + \sum_{nonbonded} \epsilon\left[\left(\frac{R_{ij}^{min}}{r_{ij}}\right)^{12} - \left(\frac{R_{ij}^{min}}{r_{ij}}\right)^{6}\right] + \frac{q_i q_j}{4\pi\varepsilon\varepsilon_0 r_{ij}} + RT\ln\left[\sum_{nonbonded} P(r_{ij})\right]$$

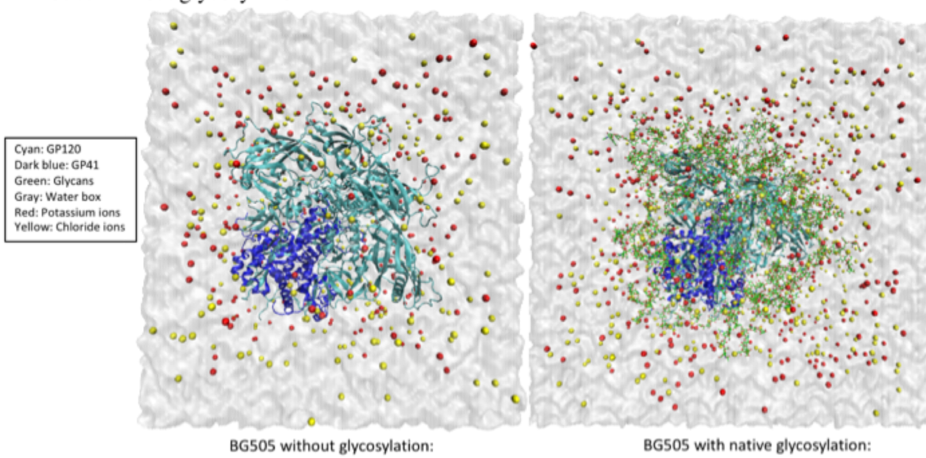
where

$$P(r_{ij}) = \begin{cases} P_{gauss}; & r_{ij} < \overline{r_{ij}} \\ 0; & r_{ij} < \overline{r_{ij}} \end{cases} \qquad P_{gauss} = \frac{1}{\sigma_{ij}\sqrt{2\pi}} exp\left[-\frac{1}{2}\left(\frac{r_{ij}-\overline{r_{ij}}}{\sigma_{ij}}\right)^2\right]$$

Large-scale MD simulations of Env ECD to investigate temporal behavior of glycan shield

5 trajectories each of more than 1μs classical MD runs, for the following three systems:

- ❑ BG505 with M9 glycosylation
- ❑ BG505 with native glycosylation
- ❑ BG505 without glycosylation



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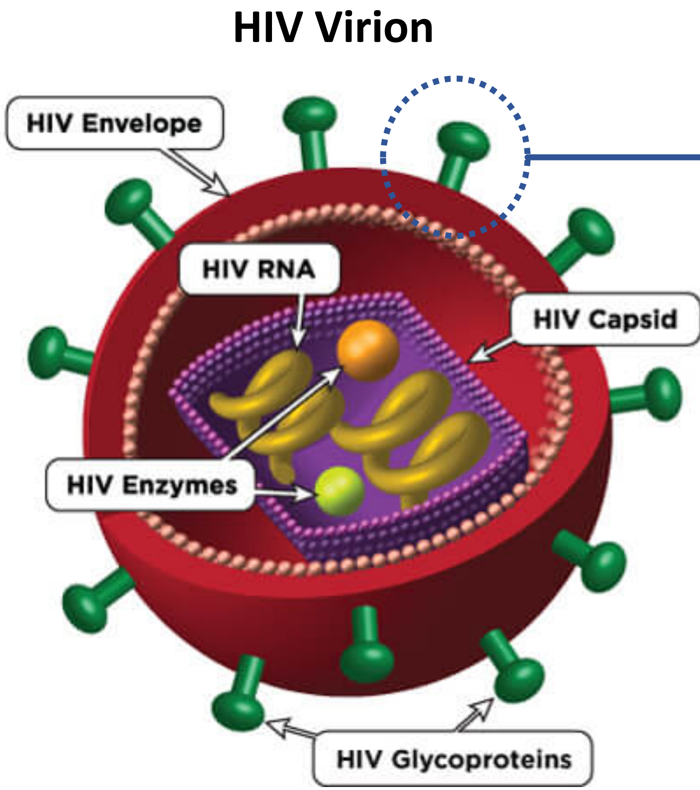

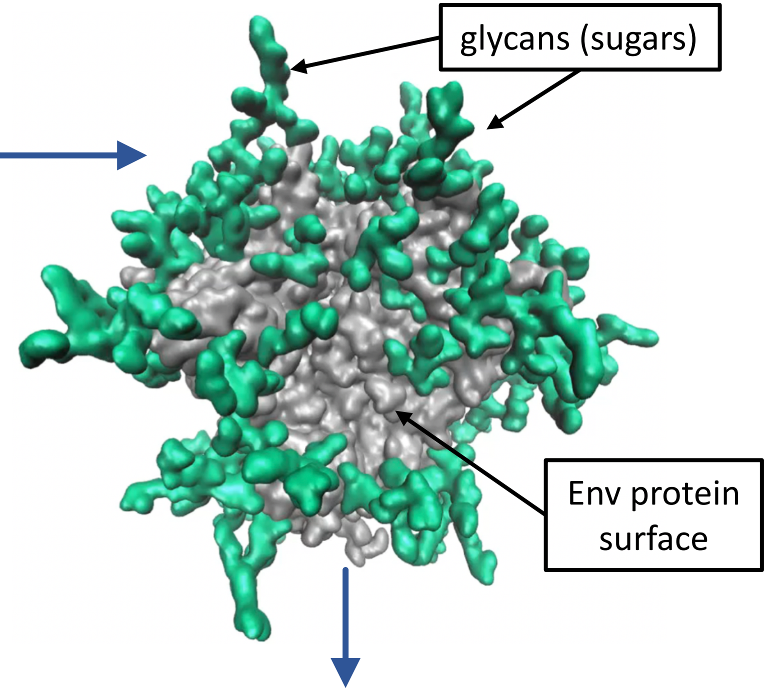

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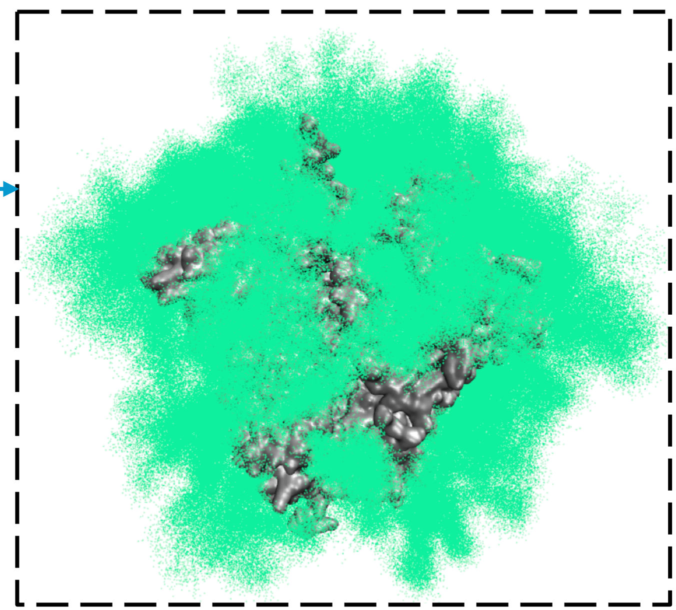

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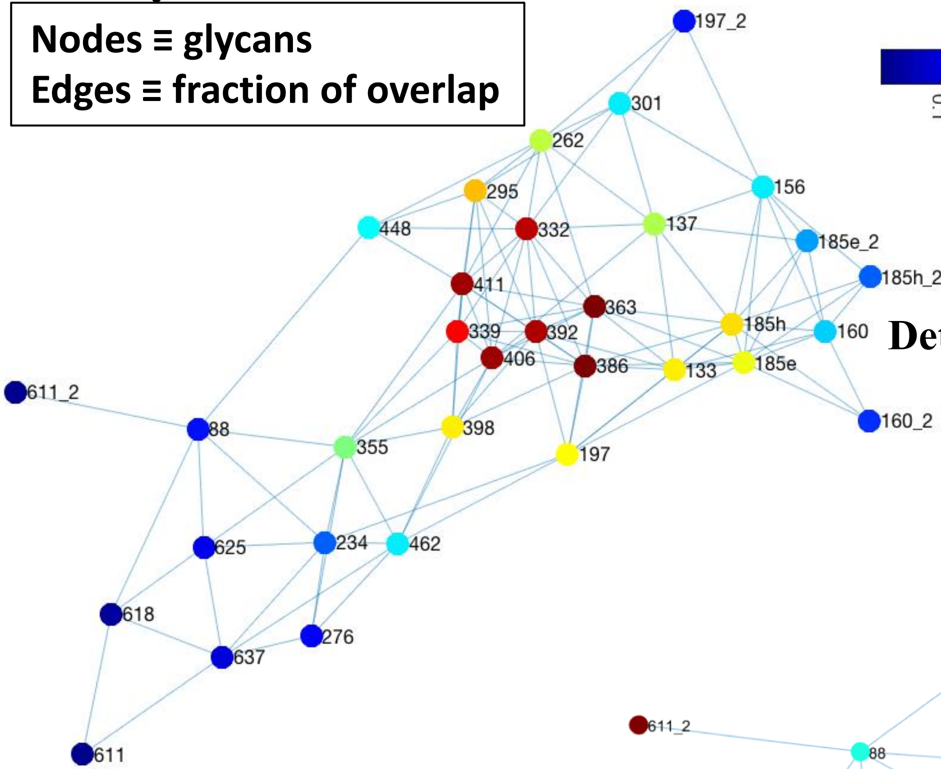
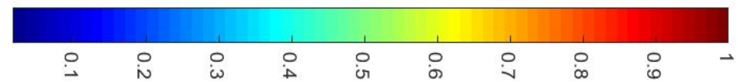
Immunologically relevant local and global properties of glycan shield

Glycan network:

Nodes ≡ glycans
Edges ≡ fraction of overlap



Eigenvector centrality



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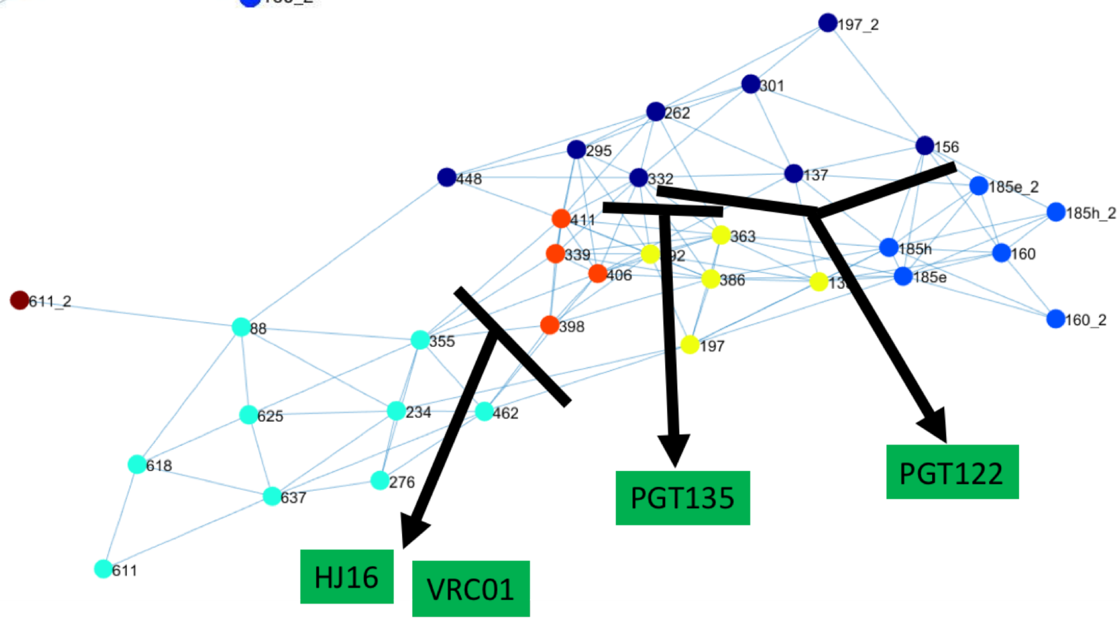

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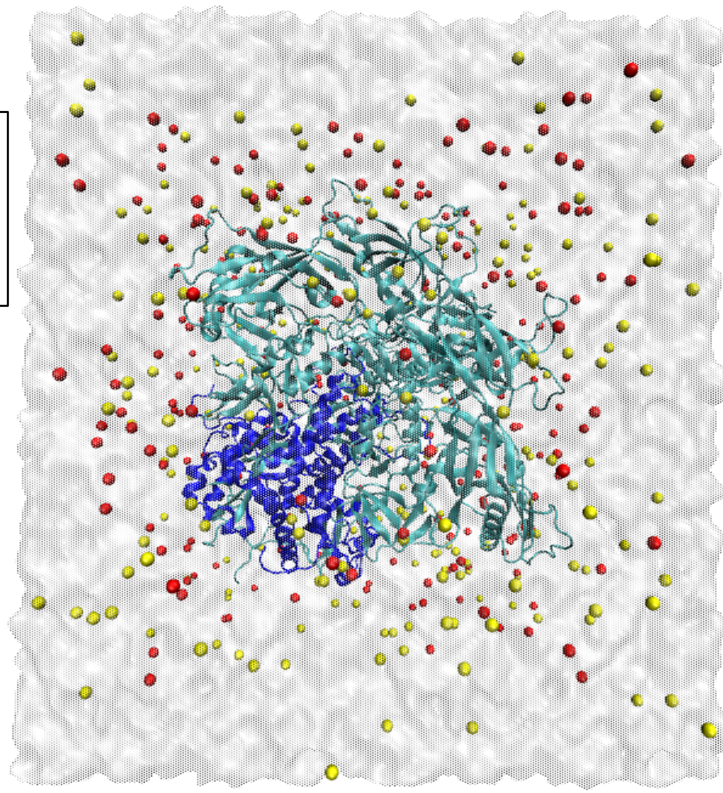
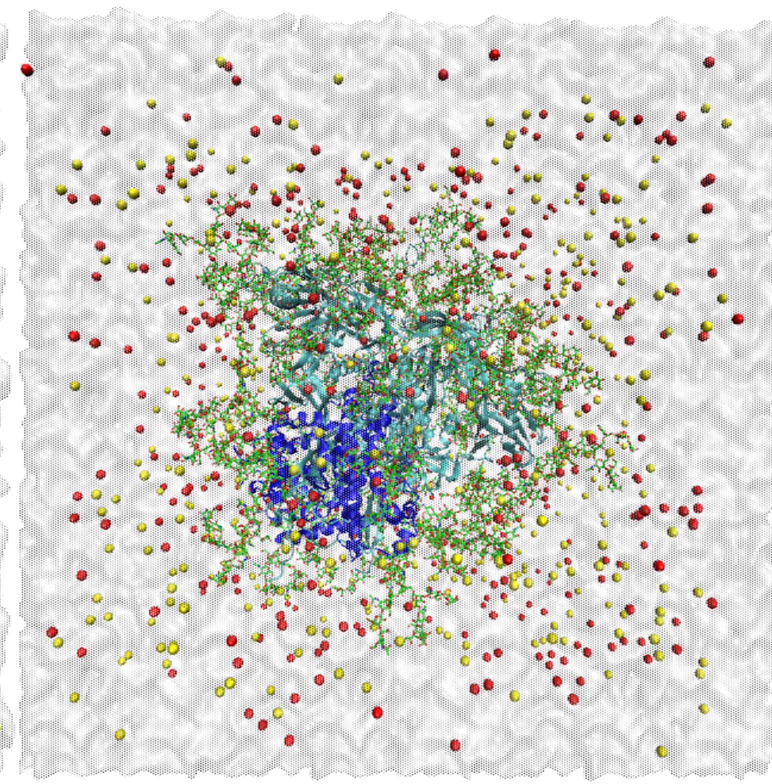
Cyan: GP120
Dark blue: GP41
Green: Glycans
Gray: Water box
Red: Potassium ions
Yellow: Chloride ions



BG505 without glycosylation



BG505 with native glycosylation